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Personal experience

Use of α-tocopherylquinone in the treatment of ulcerative colitis

SUMMARY The effect of α-tocopherylquinone (α-TQ) and a low fat diet on a patient with chronic continuous ulcerative colitis was described. The patient's condition improved dramatically with both colonic and extraintestinal manifestations of the disease greatly reduced with doses of α-TQ of 3·0 g/day (50 mg/kg/d) or greater. Withdrawal of α-TQ for periods of one to two days produced recurrence of inflammation which was again reduced upon re-introduction of α-TQ.

By the winter of 1982 I had had severe, continuously active ulcerative colitis for five years. Medical management, including corticosteroids, sulphasalazine, tetracycline, and bactrim had proved ineffective and each time the dose of prednisone was reduced below 30 mg/day the symptoms of the disease became severe. Subsequent experiments to determine the effect of diet and of dietary supplements on the course of the disease indicated that a very low fat diet supplemented with vitamin E and ferrous gluconate could reduce the severity of the symptoms sufficiently for corticosteroids to be discontinued. As vitamin E alone or ferrous gluconate alone had no beneficial effect the active substance was postulated to be a product of *in vivo* interaction of vitamin E and iron. The most likely product of such an interaction is α-tocopherylquinone (α-TQ)[1] and this substance was tested for its ability to suppress the activity of ulcerative colitis.

Methods

DL-α-tocopherylquinone was produced by oxidation of 4·7 g DL-α-tocopherol (USP) (provided by Roche Chemical Division, Hoffmann-La Roche Inc, Nutley, New Jersey) with 14·1 g $FeCl_3$–$6H_2O$ in 700 ml absolute ethanol at 50°C for 50 minutes. After dilution with water and extraction with diethyl ether the resultant oil was dissolved in absolute ethanol and water added until a yellow oil separated. Analysis by high performance liquid chromatography and ultraviolet spectroscopy indicated that this product contained more than 90% DL-α-TQ and no DL-α-tocopherol. D-α-tocopherylquinone was produced by an analogous procedure from commercially purchased mixed tocopherols containing approximately 65% D-α-tocopherol, 5% other tocopherols and 30% other vegetable oils.

Results

After two years of adhering to a low fat diet (containing 2700 Kcal/day,

Table *Change in condition with increasing dose of α-TQ**

Day of expt	0	26	68	93	117	184	261	330	367	442
Days on dose before testing	—	19	17	7	9	18	70	33	17	44
α-TQ (g/day)†	0	0·3	0·9	1·5	2·4	3·0	3·6	5·4	4·0	4·5
Hgb (g/dl)	10·1	11·9	11·7	12·4	11·6	14·3	14·4	15·0	15·1	16·0
Hct (%)	32·0	32·0	35·0	37·0	37·0	44·0	43·9	48·1	46·0	46·2
Protein (g/dl)‡	4·2	5·0	5·0	5·3	5·0	5·5	5·7	5·8	6·2	6·2
Stools/day	6–8	4–6	4–6	3–4	3–4	3	2–3	2–3	2–3	2–3

*Patient was a 34 year old, 60 kg white male. †Dosage is given as total weight of oil as separated from ethanol by the addition of water. This product contains approximately 20% (by volume) ethanol and water. D-α-TQ was used until day 334 when it was replaced by DL-α-TQ. ‡Total serum protein. During the course of the experiment the low fat diet was maintained, ferrous gluconate was reduced to 975 mg/d on day 70 and to 325 mg/d on day 390, naproxen was discontinued on day 121 and sulphasalazine was discontinued on day 195.

80% carbohydrate, 17% protein, 3% fat by weight, calculated from USDA food composition Tables) and supplementation with 3000 IU vitamin E, 1·95 g ferrous gluconate, 1·50 g sulphasalazine and intermittent use of 750 mg/day naproxen I was experiencing six to eight semiformed stools per day with frequent gross blood, moderately severe polyarticular arthritis, abdominal cramps, and skin lesions on my face and scalp. Colonoscopy before the administration of α-TQ revealed mild inflammation in the rectum and severe inflammation in the sigmoid and descending colon with ulceration, pseudopolyposis and an edematous and friable mucosa. Multiple biopsy specimens showed crypt abcesses and a prominent inflammatory cell infiltration of the lamina propria. The changes in my condition with increasing dosage of α-TQ can be seen in the Table. There was dramatic improvement until the only remaining symptom was a mild facial rash. This was the first time in the entire seven year course of the disease that I was free of symptoms except when on high doses of corticosteroids.

Colonoscopy on day 389 of the experiment revealed a normal appearing rectum except for the presence of one pseudopolyp. The sigmoid and descending colon showed multiple pseudopolyps, many with eroded tips. No ulceration was noted. The mucosa showed slight edema and was not friable. Multiple biopsies showed a normal appearing mucosa with scattered lymphocytes in the lamina propria, consistent with slight inflammation.

Several times during the course of this experiment α-TQ was discontinued for one to two days and each time a recurrence of inflammation was noted with more frequent and looser stools and intensification of the skin lesions. Resumption of the current dose of α-TQ led in all cases to a rapid regression of these symptoms.

No adverse effects of α-TQ administration were noted. There were no abnormalities in blood counts or chemistries including serum liver enzyme concentrations and prothrombin time.

Discussion

The beneficial effect of α-TQ may have been due to an anti-inflammatory or immunosuppressive action or to a direct effect on the colonic flora. As

incidental inflammation not associated with the ulcerative colitis was unaffected by α-TQ an anti-inflammatory action is unlikely. The rapid recurrence of inflammation upon discontinuation of α-TQ and the limited effectiveness of drugs such as azathioprine[2–4] suggest that immunosuppression was not the mechanism of action. α-tocopherylquinone may have acted by inhibiting the growth or metabolism of colonic bacteria. The adverse effect of dietary fat and the anti-vitamin K activity of α-TQ[5 6] suggest that α-TQ might have acted by inhibiting the production of vitamin K dependent bacterial metabolites of bile acids or cholesterol which, in genetically susceptible individuals, may be responsible for the inflammation of ulcerative colitis.

Analysis of the DL-α-TQ was carried out by Dr James G Hamilton, Hoffmann-La Roche Inc, Nutley, New Jersey.

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